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The Role of *Chlamydia trachomatis* in Prostatitis Syndrome – Our Experience in Diagnosis and Treatment

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SUMMARY Since the beginning of 1999, over 1500 patients with symptoms of chronic prostatitis were examined at Dr. Fran Mihaljević University Hospital for Infectious Diseases in Zagreb. In almost all of these patients urethral swabs and quantitative segmented bacteriologic cultures and microscopy of expressed prostatic secretion (EPS) or voided bladder urine$_3$ (VB_3) were performed as described by Meares and Stamey. Urethral swabs, EPS or VB_3 were examined for the presence of *Chlamydia (C.) trachomatis* by McCoy culture and Lugol stain or by immunofluorescent typing with monoclonal antibodies. In the majority of patients *C. trachomatis* was demonstrated in parallel in EPS or VB_3 by DNA/RNA hybridization method. Normal white blood cell count viewed *per* high power field <10 was found in 362 (68%) of 536 patients with symptoms of chronic prostatitis and *C. trachomatis* detected in EPS or VB_3. These findings additionally suggest that *C. trachomatis* can be suspected as a causative pathogen in all categories of chronic prostatitis syndrome. Furthermore, this paper summarizes the results of five previously published clinical studies on the efficacy and tolerability of various treatment schemes for chronic chlamydial prostatitis, conducted from the beginning of 1999 until the end of 2003.

KEY WORDS: *Chlamydia trachomatis*, prostatitis syndrome, diagnosis, treatment

INTRODUCTION

Since the beginning of 1999, as part of three scientific research projects of the Ministry of Science, Education and Sports of the Republic of Croatia (Urogenital infections caused by *Chlamydia trachomatis*, No. 143004; Etiology and treatment of chronic prostatitis, No. 0108149; and Clinical significance of *Ureaplasma urealyticum* and *Mycoplasma hominis*, No. 0143003), we have been prospectively investigating prostatitis syndrome and urogenital infections caused by *Chlamydia (C.) trachomatis* at Outpatient Department of Urogenital Infections and Sexually Transmitted Diseases, Dr. Fran Mihaljević University Hospital for Infectious Diseases, Zagreb.

Prostatitis syndrome refers to a number of conditions that are presented with urethral symptoms,

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prostatic symptoms, sexual dysfunction and other symptoms like fatigue, myalgia, headache, etc. (1). It is diagnosed by clinical symptoms and signs, expressed prostatic secretion (EPS) microscopy, and culture of EPS and segmented urine samples (VB_1, VB_2, VB_3) according to Meares and Stamey (2). According to the duration of symptoms, prostatitis is described as acute or chronic when symptoms are present for at least 3 months (3).

The classification of prostatitis syndrome according to Drach *et al*. differentiates between:

1) acute bacterial prostatitis (ABP);

2) chronic bacterial prostatitis (CBP);

3) nonbacterial prostatitis; and

4) prostatodynia (4).

A new classification of prostatitis syndrome has been introduced according to the US National Institutes of Health, 1995:

1) ABP, acute infection of the prostate;

2) CBP, recurrent infection of the prostate;

3) chronic pelvic pain syndrome (CPPS), no demonstrable infection, subdivided into:

(a) inflammatory CPPS, chronic abacterial prostatitis, white blood cells in EPS/VB_3, and

(b) non-inflammatory CPPS, prostatodynia, no white blood cells in EPSs/VB_3;

4) asymptomatic inflammatory prostatitis (AIP), no subjective symptoms, detected either by prostate biopsy or by the presence of white blood cells (WBC) in prostate secretion during evaluation for other disorders (5).

C. trachomatis is the most common bacterial pathogen of sexually transmitted diseases causing acute and chronic recurrent but also persistent infections. *C. trachomatis* is a common bacterial pathogen causing prostatitis (6,7).

The aim of this paper was to concisely summarize the results of our studies on the diagnosis and treatment of chronic prostatitis caused by *C. trachomatis*.

PATIENTS AND METHODS

The study was conducted at Outpatient Department of Urogenital Infections and Sexually Transmitted Diseases, Dr. Fran Mihaljević University Hospital for Infectious Diseases, Zagreb, Croatia since March 1, 1999, and is still ongoing. The Hospital Ethics Committee approved the study.

Patients

We examined more than 1500 patients older than 18 with chronic prostatitis syndrome. The majority of patients presented to our Outpatient Department for the symptoms of urogenital infection, and only some for the symptoms and laboratory findings of their sexual partner, reactive arthritis, infertility, or for fear from having contracted a sexually transmitted disease. The patients included in the study complained of urethral symptoms (irritative voiding dysfunction, urinary urgency, frequency, nocturia, dysuria), prostatic symptoms (pain and discomfort in the low back and in the perineal, suprapubic, penile, scrotal, or groin areas) and sexual symptoms (pain during or after ejaculation or erectile dysfunction). In all patients clinical symptoms were present for at least 3 months. Ultrasound examination showed no evidence of anatomical abnormality of the genitourinary tract in these patients.

Patients with hypersensitivity to macrolides or tetracyclines, severe renal or hepatic impairment (AST and/or ALT levels twice above the upper limit) as well as patients who had received any oral antibiotic 2 weeks prior to study enrolment and patients with chronic diarrheal diseases or other gastrointestinal conditions that may have affected drug absorption, were excluded from the studies that investigated the efficacy and tolerability of various treatment schemes for the treatment of chronic prostate infection caused by *C. trachomatis*.

Diagnostic criteria

The inclusion criteria for *C. trachomatis* prostatitis were the presence of clinical symptoms of chronic prostatitis, presence of *C. trachomatis* in EPS or voided bladder urine collected immediately after prostatic massage (VB_3), absence of *C. trachomatis* in urethral swabs and absence of other possible pathogens of chronic prostatitis in urethral swab specimens, VB_1 (first void urine), VB_2 (midstream urine), EPS or VB_3.

Methods

The following data were obtained for each patient: medical history, clinical status including digitorectal prostatic examination, urethral swab specimens and selective samples of urine, and EPS, according to the 4-glass localization test (Meares and Stamey's localization technique). Urethral swab specimens, EPS or VB_3 were examined for the presence of *C. trachomatis, Ureaplasma (U.) urealyticum, Mycoplasma (M.) hominis and Trichomonas (T.) vaginalis.* Quantitative segmented cultures and bacterial identification in three voided samples and EPS were performed

at Laboratory of Clinical Microbiology, Dr. Fran Mihaljević University Hospital for Infectious Diseases using standard microbiology methods.

The diagnosis of urogenital mycoplasma was confirmed by semiquantitative culturing and antimicrobial susceptibility test, Mycoplasma duo, and S.I.R. Mycoplasma test (Bio-Rad-Laboratories).

The diagnosis of *T. vaginalis* was confirmed by culture on Diamond modified medium (8).

In all patients, the isolation of *C. trachomatis* was performed at Croatian Institute of Public Health, Zagreb, Croatia. From the beginning of our study until December 31, 2002, *C. trachomatis* was proved by isolation on McCoy culture and Lugol stain. From January 1, 2003 to date, *C. trachomatis* was proved by isolation on McCoy culture and by immunofluorescent typing with monoclonal antibodies. In the majority but not all patients, *C. trachomatis* was proved by DNA/RNA Digene hybridization method, which was performed at Laboratory of Molecular Diagnosis, Dr. Fran Mihaljević University Hospital for Infectious Diseases.

Clinical efficacy and tolerability of administered drug as well as possible adverse events were evaluated during, at the end, and at 4-6 weeks of therapy completion.

Clinical response definitions:

cure, complete resolution of urethral, prostatic and sexual symptoms;

improvement, incomplete resolution of urethral, prostatic or sexual symptoms, but no need for additional therapy; and

failure, no apparent response or progression of urethral, prostatic or sexual symptoms, or additional antibiotic therapy needed.

Bacteriologic efficacy of the administered drug was evaluated at 4-6 weeks of therapy completion using methods identical to those used on study enrolment.

Bacteriologic response definitions:

eradication, eradication of *C. trachomatis* at post-treatment visit; and

persistence, persistence of *C. trachomatis* at post-treatment visit.

Antimicrobial treatment

Study 1. Azithromycin was administered to patients with chronic chlamydial prostatitis, in a total dose of 4.5 g for 3 weeks, given as a 3-day therapy of 1x500 mg at regular time intervals of 4 days. The patients' sexual partners were treated at the same time (9).

Study 2. Patients were randomized according to a computerized randomization list to receive a total dose of 4.5 g of azithromycin given as 3-day therapy of 1x500 mg weekly for 3 weeks, or clarithromycin 500 mg b.i.d. for 15 days. The patients' sexual partners were treated at the same time (10).

Study 3. Patients were randomized according to a computerized randomization list to receive a total dose of 4.5 g of azithromycin given as 3-day therapy of 1x500 mg weekly for 3 weeks, or ciprofloxacin 500 mg b.i.d. for 20 days. The patients' sexual partners were treated at the same time (11).

Study 4. Patients were randomized according to a computerized randomization list to receive a total dose of 4.5 g of azithromycin given as 3-day therapy of 1x500 mg weekly for 3 weeks, or a total dose of 6.0 g of azithromycin given as 3-day therapy of 1x500 mg for 4 weeks. The patients' sexual partners were treated at the same time (12).

Study 5. Patients were randomized according to a computerized randomization list, in a 2/1 ratio, azithromycin/doxycycyline, to receive a total dose of 4.0 g of azithromycin given as a single 1-day therapy of 1x1000 mg weekly for 4 weeks or doxycycline 100 mg b.i.d. for 28 days. The patients' sexual partners were treated at the same time (13).

RESULTS

Through summarized results of our studies, already published in various journals, we present some of our most relevant findings.

Etiology of chronic prostatitis (14) – the role of unusual pathogens in prostatitis syndrome (15)

A total of 1442 patients with symptoms of chronic prostatitis were examined during a 4-year period at Outpatient Department of Urogenital Infections, Dr. Fran Mihaljević University Hospital for Infectious Diseases, Zagreb, Croatia. An infectious etiology was determined in 1070 (74.21%) patients. Inflammatory finding (>10 WBCs/HPF) was detected in EPS or VB_3 in 561 (52.4%) of these 1070 patients.

Normal finding of <10 WBCs/HPF was recorded in 362 (67.54%) of 536 patients with symptoms of chronic prostatitis and *C. trachomatis*, 51 (33.77%) of 151 patients with *T. vaginalis* and 40 (55.56%) of 72 patients with *U. urealyticum* detected in EPS or VB_3. *Escherichia (E.) coli* was

the causative pathogen in 95, *Enterococcus* in 68, *Proteus (P.) mirabilis* in 37, *Klebsiella (K.) pneumoniae* in 16, *Streptococcus (S.) agalactiae* in 19, and *Pseudomonas (P.) aeruginosa* in three patients with chronic prostatitis. Other patients had mixed infection. In patients with chronic bacterial prostatitis caused by *E. coli*, *P. mirabilis, K. pneumoniae, Enterococcus or S. agalactiae*, inflammatory finding was regularly recorded in EPS or VB_3.

In all patients, *C. trachomatis* was detected in urethral swab/EPS/VB_3 by isolation on McCoy culture, until December 31, 2002 by Lugol stain, and from January 1, 2003 by immunofluorescent typing with monoclonal antibodies. In the majority but not all patients, *C. trachomatis* was proved in EPS/VB_3 by DNA/RNA Digene hybridization method. When EPS/VB_3 originated from the same sample, *C. trachomatis* was detected by two different methods, and comparison of the results thus obtained showed that *C. trachomatis* was three times more frequently detected by isolation on McCoy culture and using Lugol stain than by DNA/RNA hybridization, i.e. as frequently detected by isolation on McCoy culture as by immunofluorescent typing with monoclonal antibodies and DNA/RNA hybridization.

Antimicrobial treatment for chronic prostatitis caused by *C. trachomatis*

Study 1. Azithromycin in the treatment of chronic prostatitis caused by *Chlamydia trachomatis* (9).

The study included 46 patients older than 18 with symptoms of chronic prostatitis, inflammatory findings, and presence of *C. trachomatis* in EPS or VB_3. *C. trachomatis* was confirmed by isolation on McCoy culture and by Lugol stain. Patients were treated with a total dose of 4.5 g of azithromycin for 3 weeks, given as 3-day therapy of 1x500 mg at regular 4-day intervals. Bacterial eradication occurred in 40/46 (86.99%) and disappearance of symptoms in 30/46 (65.21%) patients.

Study 2. Comparative analysis of azithromycin and clarithromycin efficacy and tolerability in the treatment of chronic prostatitis caused by *Chlamydia trachomatis* (10).

The study included 123 patients older than 18 with symptoms of chronic prostatitis, inflammatory findings and presence of *C. trachomatis* confirmed by DNA/RNA Digene hybridization in EPS or voided urine collected immediately after prostatic massage. The patients were randomized to receive a total dose of 4.5 g of azithromycin for 3 weeks, given as 3-day therapy of 1x500 mg weekly or clarithromycin 500 mg b.i.d. for 15 days. In the group of patients with chronic chlamydial prostatitis, the eradication rate (azithromycin 37/46 and clarithromycin 36/45) and clinical cure rate (azithromycin 32/46 and clarithromycin 32/45) did not differ significantly according to the drug administered (p>0.05). In the group of patients with asymptomatic chlamydial prostatitis, the eradication rate (azithromycin 11/16 and clarithromycin 10/15) did not differ significantly according to the drug administered (p=1.00; OR=1.1).

Study 3. Comparative analysis of azithromycin and ciprofloxacin in the treatment of chronic prostatitis caused by *Chlamydia trachomatis* (11).

The study included 89 patients aged >18 years with symptoms of chronic prostatitis, inflammatory findings and presence of *C. trachomatis* confirmed by DNA/RNA Digene hybridization method and/or isolation on McCoy culture and Lugol stain in EPS or in voided urine collected immediately after prostatic massage. The patients were randomized to receive a total dose of 4.5 g of azithromycin for 3 weeks, given as 3-day therapy of 1x500 mg weekly or ciprofloxacin 500 mg b.i.d. for 20 days. A significantly higher eradication rate (36/45 *vs.* 17/44; p=0.0002) and clinical cure rate (31/45 *vs.* 15/44; p=0.0021) were achieved in the group of patients treated with azithromycin than in the ciprofloxacin group.

Study 4. Azithromycin: 4.5- or 6.0-gram dose in the treatment of patients with chronic prostatitis caused by *Chlamydia trachomatis* – a randomized study (12).

The study included 89 patients older than 18 diagnosed with chronic chlamydial prostatitis. *C. trachomatis* was confirmed by isolation on McCoy culture and by Lugol stain. Patients were treated with a total dose of 4.5 g of azithromycin given as 3-day therapy of 1x500 mg weekly for 3 weeks, or a total dose of 6.0 g of azithromycin given as 3-day therapy of 1x500 mg for 4 weeks. In the group of patients with chronic chlamydial prostatitis, the clinical cure rate (32/46 *vs.* 31/43; p=0.97) and eradication rate (37/46 *vs.* 35/43; p=1) did not differ significantly according to the total dose (4.5 g or 6.0 g) of azithromycin administered.

Study 5. Comparative randomized pilot study of azithromycin and doxycycline efficacy in the treatment of prostate infection caused by *Chlamydia trachomatis* (13).

The study included 125 adult patients aged >18 with symptoms of chronic prostatitis and prov-

Table 1. Etiology of chronic prostatitis

Microorganism confirmed in EPS or VB_3	Patients		
	>10 WBC/HPF in EPS No.	<10 WBC/HPF in EPS No.	Total No. (%)
Chlamydia trachomatis	174	362	536 (37.17)
Trichomonas vaginalis	100	51	151 (10.47)
Ureaplasma urealyticum	32	40	72 (4.99)
Escherichia coli	90	5	95 (6.59)
Enterococcus	52	16	68 (4.72)
Proteus mirabilis	35	2	37 (2.57)
Klebsiella pneumoniae	14	2	16 (1.11)
Streptococcus agalactiae	12	7	19 (1.32)
Pseudomonas aeruginosa	2	1	3 (0.21)
Mixed infection	50	23	73 (5.06)
None	91	281	372 (25.79)
Total	652	770	1442 (100.00)

EPS= expressed prostatic secretion; VB_3= postprostatic massage urine

en presence of *C. trachomatis*. The presence of *C. trachomatis* was confirmed in EPS or in voided urine collected immediately after prostatic massage by DNA/RNA hybridization and/or isolation on McCoy culture, and then by immunofluorescent typing with monoclonal antibodies. The patients were randomized at a 2/1 ratio of azithromycin/doxycycline to receive a total dose of 4.0 g azithromycin over 4 weeks, given as a single dose of 1x1000 mg weekly for 4 weeks or doxycycline 100 mg b.i.d. for 28 days. In the group of patients with chlamydial infection of the prostate, there was no significant difference in the eradication rate (azithromycin 65/82 *vs.* doxycycline 33/43; p=0.82) and clinical cure rate (azithromycin 56/82 *vs.* doxycycline 30/43; p=0.94) according to the antimicrobial administered.

DISCUSSION AND CONCLUSION

Considering important biological features of *C. trachomatis* for establishing balance with the host and causing latent asymptomatic or oligosymptomatic persistent infections leading to various cellular inflammatory responses, *C. trachomatis* can be suspected as a causative pathogen in all categories of prostatitis syndrome, regardless of classification, as described in the last categorization (NIDDK). From March 1, 1999 to the present, urethral swabs and quantitative segmented bacteriological cultures and microscopy of EPS or VB_3 as described by Meares and Stamey were performed in almost all our patients with symptoms of chronic prostatitis. Urethral swabs and EPS or VB_3 of all patients were investigated for the presence of *C. trachomatis*, *U. urealyticum*, *M. hominis* and *T. vaginalis*. The results of these studies which evaluated 1442 patients with inflammatory as well as noninflammatory pelvic pain syndrome showed they may have had *C. trachomatis* in their prostate. In our study, normal WBC/HPF (<10) was found in 362 (68%) of 536 patients with symptoms of chronic prostatitis and *C. trachomatis* detected in EPS or VB_3.

As there is no diagnostic method specific enough to be recommended as a method of *C. trachomatis* detection in EPS/VB_3, we consider our findings, with corresponding results obtained by isolation of *C. trachomatis* in EPS/VB_3 by McCoy culture and by immunofluorescent typing with monoclonal antibodies and DNA/RNA hybridization, significant and useful for investigation of chlamydial infections of the prostate.

Assessment of clinical and bacteriological efficacy and tolerability of a total dose of 4.0, 4.5 or 6.0 g of azithromycin for 3 or 4 weeks, ciprofloxacin 500 mg b.i.d. for 20 days, clarithromycin 500 mg b.i.d. for 15 days, and doxycycline 100 mg b.i.d. for 28 days pointed to the following conclusions:

1. in patients with chlamydial prostatitis and in patients with inflammatory or noninflammatory chronic pelvic pain syndrome, ciprofloxacin is not recommended if *C. trachomatis* is suspected;
2. although clarithromycin has been shown to be effective and safe in the treatment of chlamydial infection of the prostate, it is not registered for the treatment of urogenital infections and cannot be used in daily routine for the treatment of chlamydial prostatitis and other chlamydial urogenital infections; and
3. in patients with chlamydial infection of the prostate, the drugs of choice are azithromycin in a

total dose of 4.0, 4.5 or 6.0 g given periodically for 3 or 4 weeks, or doxycycyline 100 mg b.i.d. for 4 weeks.

We are fully aware that the research conducted so far has its disadvantages and flaws. To our opinion, the major disadvantages are that clinical symptoms of prostatitis have not been followed according to the Chronic Prostatitis Symptom Index (NIH-CPSI) and that clinical and bacteriological evaluation of therapeutic efficacy at 6 months of treatment completion is lacking (16,17).

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